A STUDY OF CARDIAC DYSFUNCTION IN CIRRHOTIC PATIENTS

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CERTIFICATE

This is to certify that this dissertation entitled "A Study of Cardiac Dysfunction in Cirrhotic Patients" submitted by Dr.P.Ratnakar Kini to the faculty of Medical Gastroenterology, The Tamilnadu Dr.MGR Medical University, Guindy, Chennai-600032, in partial fulfillment of the requirement for the award of DM., Degree Branch IV (Gastroenterology) is a bonafide work carried out by her under my direct supervision and guidance.

Prof.S.Jeevan Kumar,MD.,DM.,
Professor and HOD,
Department of Digestive Health and Diseases,
Government Peripheral Hospital, Anna Nagar,
Attached to Kilpauk Medical College,
Chennai-600010

Dr.V.Kanagasabai MD
Dean
Government Kilpauk Medical College, Kilpauk,
Chennai-600010

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INTRODUCTION

Liver cirrhosis is associated with a wide range of cardiovascular abnormalities. This was first described by Kowalski and Abelmann who noted a higher resting cardiac output and decreased systemic vascular resistance in patients with cirrhosis[1, 2]. However, despite the hyperdynamic circulation, impaired ventricular contractility in response to stimuli was described in cirrhotic patients[3-7]. These abnormalities were initially thought to be a manifestation of latent alcoholic cardiomyopathy. But in the mid-1980s, studies in nonalcoholic patients and in experimental animal models showed a similar pattern of blunted cardiac contractile responsiveness[8-10]. Thus these cardiovascular changes are now termed 'cirrhotic cardiomyopathy'[11-14].

The prevalence of cirrhotic cardiomyopathy remains unknown at present. Features include structural, histological, electrophysiological, systolic and diastolic dysfunction. Multiple factors are considered as responsible, including impaired beta-adrenergic receptor signal transduction, abnormal membrane biophysical characteristics, and increased activity of cardiodepressant systems mediated by cGMP[15].

Overt heart failure is not generally a feature of cirrhotic cardiomyopathy, because the associated marked vasodilatation

accompanying the hyperdynamic circulation significantly reduces ventricular afterload. However, major stresses on the cardiovascular system such as liver transplantation, infections and insertion of transjugular intrahepatic portosystemic shunts (TIPS) can unmask the presence of cirrhotic cardiomyopathy and thereby convert latent to overt heart failure. Cirrhotic cardiomyopathy may also contribute to the pathogenesis of hepatorenal syndrome and circulatory failure in liver cirrhosis[15].

Diastolic dysfunction is present in the vast majority of patients with cirrhotic cardiomyopathy, and that simple echocardiographic indices such as the E/A ratio may detect diastolic dysfunction even at rest. This may therefore represent the best available screening test to diagnose cardiac dysfunction[16].

Due to the limited number of human studies, the management of cirrhotic cardiomyopathy remains largely empirical. Treatment of this condition is mainly supportive. Orthotropic liver transplantation appears to improve or normalize the condition, generally after a period of several months[17]. If overt heart failure develops in these patients, then the same general treatment principles of noncirrhotic congestive heart failure apply, including bed rest, salt restriction, oxygen, diuretics, and careful preload and afterload reduction [14].

LITERATURE REVIEW

Cirrhosis is a gradually developing, chronic disease of the liver. It is the irreversible consequence and final stage of various chronic liver diseases of different etiology or the result of long-term exposure to various noxious agents. Aretaeus (2nd century AD) coined the term “skirros”, because he thought that inflammation of the liver led to its hardening (skirros).

The first accurate report on cirrhosis was given by R.T.H. Laennec (1819). Because of the yellow colour of the liver (kirros), he coined the term cirrhosis. The extent of the morphological changes depends on the cause and stage of cirrhosis. Accordingly, there is a wide spectrum of morphological findings and clinical symptoms. The variations of this disease range from symptom-free conditions, noncharacteristic complaints and different laboratory findings through to life-threatening complications.

Cirrhosis of liver can be classified either etiologically or morphologically. The etiological classification is based on the underlying cause which includes alcohol, hepatitis B and hepatitis C infections, metabolic disorders like Wilson disease, nonalcoholic fatty liver disease and also due to autoimmune hepatitis. When no cause is found it is called as cryptogenic cirrhosis. Morphological classification is based on the size of

the nodules. It could be micronodular if the nodules are less than 3 mm, macronodular if they are more than 3 mm and mixed type if both are found. The mixed type is the transition form from micronodular to macronodular cirrhosis.

Cirrhosis of the liver is a disease found all over the world, affecting all races, age groups and both sexes. The incidence is about 240/million inhabitants/year. The increasing mortality rate runs parallel to regional alcohol consumption. This correlation between alcohol consumption and mortality as well as morbidity due to cirrhosis applies equally to men and women. The slight decrease in mortality in some countries observed during the past 10 -15 years may be due to more effective prophylaxis and improved treatment options for complications**.**

Hemodynamic changes in cirrhosis

Portal hypertension is one of the salient features of cirrhosis. Cirrhosis of the liver accounts for approximately 90% of cases of portal hypertension. Portal hypertension is a common clinical syndrome defined by a pathologic increase of portal venous pressure. As a consequence, the gradient between portal pressure (PP) and inferior vena cava pressure (IVC) (portal pressure gradient, PPG) is increased above the upper normal value of

5 mm Hg. The importance of portal hypertensive syndrome is defined by the frequency and severity of its complications, including upper gastrointestinal bleeding from ruptured gastroesophageal varices, ascites, and hepatorenal Syndrome, which represent the leading causes of death and of liver transplantation in patients with cirrhosis.

Portal hypertension is considered to be clinically significant (CSPH) when PPG, or its clinical equivalent hepatic venous pressure gradient (HVPG), exceeds 10 to 12 mm Hg, since this is the threshold for the clinical manifestations of portal hypertensive syndrome to appear. The vast majority of patients with cirrhosis develop CSPH along the course of the disease, and data from a recent multicentric study indicate that CSPH is already present at diagnosis in approximately 60% of histologically proven, well-compensated cirrhosis case.

Portal hypertension is related both to vascular resistance and to portal blood flow. The fundamental hemodynamic abnormality is an increased resistance to portal flow. This may be mechanical due to the disturbed architecture and nodularity of cirrhosis or due to an obstructed portal vein. Other intra-hepatic factors such as collagenosis of the space of Disse, hepatocyte swelling and the resistance offered by portal-systemic collaterals

contribute. There is also a dynamic increase in intra-hepatic vascular resistance.

Stellate (Ito) cells have contractile properties that can be modulated by vaso-active substances. These include nitric oxide (NO) which is vasodilatory and endothelin which is a vaso-constrictor. These may modulate intra-hepatic resistance and blood flow especially at a sinusoidal level.

As the portal venous pressure is lowered by the development of collaterals deviating portal blood into systemic veins, portal hypertension is maintained by increasing portal flow in the portal system which becomes hyperdynamic. It is uncertain whether the hyperdynamic circulation is the cause or the consequence of the portal hypertension or both. It is related to the severity of liver failure. Cardiac output increases and there is generalized vasodilatation. Arterial blood pressure is normal or low.

Splanchnic vasodilatation is probably the most important factor in maintaining the hyperdynamic circulation. Azygous blood flow is increased. Gastric mucosal blood flow rises. The increased portal flow raises the oesophageal variceal transmural pressure. The increased flow refers to total portal flow (hepatic and collaterals).The actual portal flow reaching the liver is, of course, reduced. The factors maintaining the hyperdynamic splanchnic

circulation are multiple. There seems to be interplay of vasodilators and vaso-constrictors. These might be formed by the hepatocyte, fail to be inactivated by it or be of gut origin and pass through intra-hepatic or extra-hepatic venous shunts.

Endotoxins and cytokines, largely formed in the gut, are important triggers. NO and endothelin-1 are synthesized by vascular endothelium in response to endotoxin. Prostacyclin is produced by portal vein endothelium and is a potent vasodilator. It may play a major role in the circulatory changes of portal hypertension due to chronic liver disease.

Glucagon is vasodilatory after pharmacological doses but does not seem to be vaso-active at physiological doses. It is probably not a primary factor in the maintenance of the hyperkinetic circulation in established liver disease.

Cardiac and vascular changes in cirrhosis

The cardiovascular system in patients with cirrhosis or portal hypertension is abnormal. The circulation becomes hyperdynamic, characterized by increased cardiac output and decreased peripheral vascular resistance and arterial pressure. Moreover, despite the increased cardiac output at rest, with stressful stimuli such as hemorrhage, surgery or vasoactive drug administration, the ventricular response is blunted, a

condition known as cirrhotic cardiomyopathy. These cardiovascular abnormalities have been suggested to induce or aggravate several complications of cirrhosis such as renal salt and water retention, variceal bleeding, hepatopulmonary syndrome, and increased cardiovascular fragility under stress. Recent reviews have detailed the clinical aspects of hyperdynamic circulation[18, 19] and cirrhotic cardiomyopathy[20, 21, 22].

HYPERDYNAMIC CIRCULATION

Peripheral vasodilatation is central to hyperdynamic circulation and portal hypertension in cirrhosis. However, the factors directly initiating vasodilatation remain obscure. A hypothesis that has received much attention over the past three decades is the "humoral factor" theory. In cirrhosis, increased intrahepatic resistance induces portosystemic collateral formation, allowing gut-derived humoral substances to directly enter the systemic circulation without detoxification by the liver. The following gut-derived or locally-produced humoral factors have been implicated as possible mediators of peripheral vasodilatation in cirrhosis or portal hypertension.

Endocannabinoids

Endocannabinoids are lipid-like substances that act on two inhibitory G protein-coupled receptors, CB1 and CB2. The vasodilatory effect of endogenous cannabinoids in cirrhosis was first reported in 2001[23] Anandamide, an endogenous cannabinoid or endocannabinoid, is increased in monocytes of cirrhotic rats [23,24], and its receptor CB1 is also upregulated in the vascular endothelium of patients with cirrhosis [23]. Infusing monocytes isolated from cirrhotic rats into normal rats decreases the mean arterial pressure in the recipients. Furthermore, administering a CB1 receptor antagonist SR141716A to cirrhotic rats increases the total peripheral resistance[23,24], both studies demonstrated that SR141716A significantly increases the reduced arterial pressure in cirrhosis, and blocks the hypotension induced by the infusion of isolated cirrhotic monocytes into normal rats[23,24]. Batkai and colleagues also found that SR141716A decreases mesenteric blood flow and portal venous pressure in cirrhotic rats [23]. All of these data indicate that the vascular tone in cirrhosis is regulated by CB1 receptors in both the splanchnic and systemic circulations.

Besides vasodilatation, anandamide rapidly and dose-dependently induces apoptosis in primary culture-activated and in vivo-activated hepatic stellate cells, with over 70% cell death after 4 h at 25 μmol/L[25]. This effect could

alter the hepatic sinusoidal microcirculation and enhance the development of portal hypertension that leads to hyperdynamic circulation.

How does cirrhosis leads to increased endocannabinoids? Varga and co-workers found that bacterial endotoxin stimulates endocannabinoid production in cirrhosis [26]. The up regulation of CB1 receptors in cirrhotic vascular endothelium and thus increased end-organ sensitivity may also enhance endocannabinoid vasodilator tone [23].

Nitric oxide

NO has been extensively studied. It is now clear that in cirrhosis, changes in NO activity affect different vascular beds in variable ways. In the liver microcirculation, endothelial-constitutive NO synthase (eNOS or NOS3) expression is decreased in a cirrhotic rat model [27]. Simvastatin enhances hepatic nitric oxide production and decreases the hepatic vascular tone in patients with cirrhosis[28]. An NO donor[29] or NOS3 gene transfection[27], which compensates for the decreased hepatic NOS3 expression, significantly lowers the increased portal pressure in cirrhosis.

In contrast, systemic NO production is increased in cirrhotic patients and animal models [30-32]. Moreover, normalization of NO production in cirrhotic rats, by achieving normal concentrations of aortic cGMP with small doses of

the NOS inhibitor L-NAME, normalizes the decreased peripheral vascular resistance and the increased cardiac output [33]. In vitro, an NO inhibitor reverses the hyporeactivity of blood vessels from cirrhotic rats to vasoconstrictors [34].

All these results strongly support the hypothesis that increased NO production is a major factor in the peripheral arterial vasodilation of cirrhosis. Agents promoting nitric oxide production include inflammatory cytokines and endotoxin. In that regard, selective intestinal decontamination with norfloxacin partially reverses the hyperdynamic circulatory state in cirrhotic patients, suggesting a role for the endotoxin-NO pathway [35]. Where does this endotoxin come from in cirrhosis? First, alcohol is a major cause of cirrhosis in Western countries, and alcoholic gastrointestinal mucosal damage [36], could potentially facilitate transfer of bacteria into the circulation. Second, portosystemic shunting allows gut-derived bacterial endotoxins passage to the systemic circulation. Third, cirrhotic patients with portal hypertension show intestinal structural abnormalities characterized by vascular congestion and edema, which leads to increased intestinal permeability to bacterial toxins [37]. Fourth, intestinal bacterial overgrowth and bacterial translocation are increased in cirrhosis [38]. Besides endotoxins, the other possible factors stimulating NO production include cytokines such as

TNF-α, IL-1, IL-6, and IFN-γ[39-41] Among these, TNF-α has been studied the most. Lopez-Talavera et al found that anti-TNF-α antibody increases mean arterial pressure and systemic vascular resistance, and decreases cardiac index and portal pressure [42]. In 4-week BDL rats, in parallel with increased serum TNF-α, aortic NOS3 expression and serum nitrate/nitrite concentrations were increased [43].

Although the evidence is strong that the increased NOS activity in cirrhosis plays an important role in hyperdynamic circulation in cirrhosis, it remains obscure which NOS isoform is involved. The majority of previous studies have used a nonspecific NOS inhibitor to diminish NO production. However, a recent study used aminoguanidine, a preferential inhibitor of NOS2 (inducible NOS), and showed that in vivo, the hyperdynamic circulation in portal hypertensive rats is reversed [44]. But in another study aminoguanidine had no in vitro effect on the hyporeactivity of aortic rings from cirrhotic rats [45]. We have recently evaluated the activity of the L-arginine-NO pathway at different levels [43]. Although NOS2 mRNA was detectable in the cirrhotic aorta, no NOS2 protein was observed in our Western blots. It is unclear why the mRNA was not expressed as a protein. It might have been degraded or not been transcribed. It is also possible that our

method of Western blotting did not allow the detection of small amounts of NOS2 protein.

A consistent augmentation in the expression of NOS3 mRNA and protein levels is observed in cirrhotic rats. Because NOS3 can be upregulated by stimuli such as shear stress and mechanical deformation, some have suggested that hyperdynamic circulation is the cause rather than the consequence of the activation of the NO pathway [31, 46, 47]. In addition, there may be other reasons for the increased NOS3. Cirrhosis is associated with increased levels of estrogens [48,49], and these compounds have been shown to upregulate NOS3 activity[50]. Other factors which may stimulate NOS3 expression need further investigation.

What is the role of another isoform of NOS, neuronal NOS (nNOS or NOS1)? Xu and his colleagues have demonstrated that nNOS expression is significantly increased in rat cirrhotic aortae [51]. Furthermore, a nNOS-specific inhibitor, 7-nitroindazole (7-NI), significantly decreased the sodium and water retention and normalized the hyperdynamic indices such as cardiac index, mean arterial pressure, and systemic vascular resistance in these rats [51]. Biecker et al also showed that nNOS partially compensates for the absence of eNOS in producing hyperdynamic circulation in eNOS-gene knockout mice [52]. These data indicate that the nNOS isoform plays a major

pathogenic role in hyperdynamic circulation, and perhaps even in renal salt and water retention in cirrhosis.

It seems that endocannabinoids and nitric oxide may both play an important role in hyperdynamic circulation, but what is the relationship between them? The literature remains inconclusive. In a kidney study, Deutsch et al found that the vasodilatation of anandamide is NO dependent, because the NOS inhibitor L-NAME completely blocked the vasodilatory effect of anandamide, similar to a CB1 antagonist [53]. However, another study showed no effect of L-NAME infusion on the hypotensive effects of anandamide [24].

Some studies suggest the possible involvement of other humoral vasodilators, but a definitive pathogenic role for any of these substances remains elusive. This list includes: glucagons [54], prostaglandins [55], GABA[56], VIP [57], bile acids [58], endotoxin, histamine [59] and adenosine [60].

Central neural mechanisms

Although most research has focused on the humoral mediators, in recent years we and others have shown an important mechanistic role of central nervous system (CNS) activation. A decade ago, it was demonstrated that primary afferent denervation by capsaicin reversed the hyperdynamic

circulation in rats with cirrhosis or portal hypertension due to portal vein stenosis (PVS)[61]. What is the relationship between the CNS and hyperdynamic circulation in portal hypertension? Using c-fos, an immediate-early gene (whose protein product can be detected by immunohistochemistry as Fos), as a marker of central neuronal activation, it was showed that the brainstem and hypothalamic cardiovascular-regulatory nuclei are activated at the first day after PVS, whereas the hyperdynamic circulation does not start up until 3-5 days after PVS. This time sequence suggests that central neural activation is the initiating signal in the pathogenesis of hyperdynamic circulation.

Subsequently, in portal hypertensive rats, when c-fos antisense oligonucleotide was microinjected into one of the major cardiovascular-regulatory brainstem nuclei, the nucleus tractus solitarius (NTS), to block local Fos expression. This treatment completely blocked the development of the hyperdynamic circulation, i.e., abnormalities in cardiac output, mean arterial pressure and systemic vascular resistance were completely eliminated [62]. In normal control rats, c-fos antisense oligonucleotides had no effect[62]. These results indicate that central neural activation is a sine qua non for the development of the hyperdynamic circulation in portal hypertension.

The CNS, as the controller of the circulation, presumably would not arbitrarily activate the cardiovascular system without reason. This raises the question of what the initiating signal is. Likely, it is somehow related to the portal hypertension per se. Moreover, the exact route of signaling from the periphery to the CNS remains unclear. The aforementioned capsaicin study suggests that primary afferent nerves may be the signaling pathway from the periphery to the CNS [61]. A subsequent study showed that capsaicin-treated BDL rats improve the renal function and do not develop ascites[63]. Moreover, both BDL-cirrhotic and portal hypertensive rats show diminished Fos expression in NTS after capsaicin-induced denervation of the afferent nerves as neonates[63]. These observations indicate that intact primary afferent innervation is necessary for the central neuronal activation and development or maintenance of hyperdynamic circulation. Additionally, sodium retention and ascites formation is also dependent on either the presence of hyperdynamic circulation or intact afferent innervation, or both. The complex relationship between CNS activation, local or neurohormonal humoral factor stimulation, and cardiovascular disturbances in cirrhosis/portal hypertension continues to be studied in several labs.

Cirrhotic Cardiomyopathy

This syndrome was first described in the late 1960s, although for many years, it was mistakenly attributed to latent or subclinical alcoholic cardiomyopathy [64-66]. However, studies in human and animal models with nonalcoholic cirrhosis, dating from the mid-1980s showed a similar pattern of increased baseline cardiac output with blunted response to stress [21]. The clinical features of cirrhotic cardiomyopathy include blunted systolic and diastolic contractile responses to stress, in conjunction with evidence of ventricular hypertrophy or chamber dilatation and electrophysiological abnormalities including prolonged QT interval. Recent studies suggest the presence of cirrhotic cardiomyopathy may contribute to the pathogenesis of hepatorenal syndrome precipitated by spontaneous bacterial peritonitis[67],acute heart failure after insertion of transjugular intrahepatic portosystemic shunts (TIPS) [68,69], and increased cardiovascular morbidity and mortality after liver transplantation[70]. Therefore this syndrome is more than an academic curiosity, but rather an important clinical entity.

Endocannabinoids

Endocannabinoids are known to have a negative inotropic effect on cardiac contractility in both human[71] and rats[72]. The plasma level of an

endogenous cannabinoid, anandamide, is known to be increased in cirrhosis [23]. We recently demonstrated a major role for increased local cardiac production of endocannabinoids in cirrhotic cardiomyopathy [73]. This conclusion is based on the restoration of blunted contractile response of isolated left ventricular papillary muscles from BDL-cirrhotic rats after preincubation with a CB1 antagonist, AM251. Additionally, endocannabinoid reuptake blockers (VDM11 and AM404) enhance the relaxant response of cirrhotic papillary muscle to higher frequencies of contraction in an AM251-sensitive fashion, suggesting an increase in the local production of endocannabinoids acting through CB1 receptors. Other in vitro evidence suggests a main neuronal source for the increase in local production of endocannabinoids, as these effects were mostly abolished by pretreatment with the neurotoxin tetrodotoxin.

β -adrenergic signaling

Cardiac-adrenergic signaling is one of the main regulators of cardiac contractility. Adrenergic receptors increase adenylyl cyclase activity through stimulatory G proteins. Increased production of cAMP in turn results in an increase in calcium influx and contractile force mainly through activation of protein kinase A (PKA). We have previously shown that expression and

responsiveness of β-adrenergic receptors[74] as well as its post receptor signaling pathway is blunted in cardiac tissue of cirrhotic rats. Post receptor impairment was found at different levels including content and function of stimulatory Gs-proteins [75], uncoupling of the β-adrenoceptor-ligand complex from G protein [76], and responsiveness of adenylyl cyclase to stimuli [75,77].

Membrane fluidity

Biochemical and biophysical properties of the cell membrane determines the mobility of membrane-bound protein moieties. This mobility is known as membrane fluidity [78], which is shown to be an important factor in the function of a number of membrane-bound receptors including β-adrenergic receptors[79]. It was shown that membrane fluidity in cardiomyocytes from bile duct-ligated rats is decreased in association with an increase in membrane cholesterol content and cholesterol/phospholipid ratio [75]. Restoration of these abnormalities in vitro results in normalization of blunted response of β-adrenergic receptors[75]. Alterations in membrane fluidity may also play a role in abnormal function of other membrane-bound components in cirrhotic cardiomyocytes including ion channels. The significant decrease in K^+ currents through Ca^{2+}-independent transient

outward K^+ channel and the delayed rectifier current reported by Ward et al is an example that requires further investigation[80].

Nitric oxide

Nitric oxide is known to negatively regulate cardiac contractile function. It has been shown to be involved in some types of cardiac dysfunction including ischemic heart disease [81]. Balligand et al have reported that non-selective blockade of NOS augments the contractile response of rat ventricular myocytes to the β-agonist isoproterenol without affecting the baseline contractility [82]. Whether this effect is mediated by the inhibition of adenylyl cyclase activity by NO [83] or through the second messenger, cyclic guanosine monophosphate (cGMP), remains to be elucidated. Possible effects of NO on cardiac function in physiological and some pathophysiological states were extensively reviewed previously [84, 85].

As noted previously, cirrhosis is known to be associated with NO overproduction [46]. Involvement of NO overproduction in the development of cirrhotic cardiomyopathy was first reported in 1996 by Van Obbergh et al in the BDL rat. They showed that a nonselective NOS inhibitor, L-NMMA, restored the blunted contractile function of isolated heart from cirrhotic rats while it had no significant effect in control animals [86]. A similar effect was

reported in isolated left ventricular papillary muscles of cirrhotic rats. Furthermore, it was observed that iNOS and not eNOS mRNA and protein expression were significantly increased in the heart of a cirrhotic rat [39]. Increased levels of cGMP in cirrhotic ventricles and elevated serum and cardiac levels of cytokines like TNF-α suggest a cytokine/iNOS/cGMP pathway for this effect [39].

Carbon monoxide

Carbon monoxide (CO) is mainly produced in the body through the action of heme oxygenases. These enzymes are responsible for converting heme to biliverdin and CO. Like NO, CO activates soluble guanylate cyclase resulting in increased levels of cGMP [87,88]. Expression of inducible heme oxygenase (HO-1) mRNA was increased in the right ventricle in a canine model of congestive heart failure [89]. We previously reported an increase in mRNA and protein expression of HO-1 in left ventricle of bile duct-ligated rats, which was associated with an increase in left ventricular cGMP levels [90]. Furthermore, treatment of cirrhotic heart with an HO inhibitor, zinc protoporphyrin IX, restored the elevated cGMP levels [90]. These findings suggest the involvement of an HO-CO-cGMP pathway in the development of cirrhotic cardiomyopathy.

Cardiomyopathies

The cardiomyopathies are a group of diseases that primarily affect the heart muscle and are not the result of congenital, acquired valvular, hypertensive, coronary arterial or pericardial abnormalities. Two fundamental forms of cardiomyopathy are recognized: (1) a primary type, consisting of heart muscle disease predominantly involving the myocardium and/or of unknown cause; and (2) a secondary type, consisting of myocardial disease of known cause or associated with a systemic disease such as amyloidosis or chronic alcohol use. In many cases it is not possible to arrive at a specific etiologic diagnosis, and thus it is often more desirable to classify the cardiomyopathies into one of three morphologic types (dilated, restrictive, and hypertrophic) on the basis of differences in their pathophysiology and clinical presentation.

About one in three cases of congestive heart failure is due to dilated cardiomyopathy (DCM). LV and/or right ventricular (RV) systolic pump function is impaired, leading to progressive cardiac dilatation. The electrocardiogram (ECG) often shows sinus tachycardia or atrial fibrillation, ventricular arrhythmias, left atrial abnormality, low voltage, diffuse nonspecific ST-T-wave abnormalities, and sometimes intraventricular and/or AV conduction defects. Echocardiography shows LV dilatation, with

normal, minimally thickened, or thinned walls, and systolic dysfunction. Circulating levels of brain natriuretic peptide are usually elevated.

Hypertrophic cardiomyopathy (HCM) is characterized by LV hypertrophy, typically of a nondilated chamber, without obvious cause, such as hypertension or aortic stenosis. The ubiquitous pathophysiologic abnormality is diastolic dysfunction, which can be detected by Doppler tissue imaging and results in elevated LV end-diastolic pressures; the latter may be present despite a hyperdynamic, nondilated LV. The ECG commonly shows LV hypertrophy and widespread deep, broad Q waves.

The hallmark of the restrictive cardiomyopathies (RCMs) is abnormal diastolic function .The ventricular walls are excessively rigid and impede ventricular filling. In late stages systolic function is also impaired. Myocardial fibrosis, hypertrophy, or infiltration due to a variety of causes is responsible. ECG often shows low-voltage, nonspecific ST-T-wave abnormalities and various arrhythmias. Echocardiography, reveal symmetrically thickened LV walls and normal or slightly reduced ventricular volumes and systolic function; the atria are usually dilated. Doppler echocardiography typically shows diastolic dysfunction. Cardiac catheterization shows a reduced cardiac output, elevation of the RV and LV end-diastolic pressures, and a dip-and-plateau configuration of the diastolic

portion of the ventricular pressure pulses resembling constrictive pericarditis.

Cirrhotic cardiomyopathy

In the absence of specific diagnostic criteria, the exact prevalence of cirrhotic cardiomyopathy remains unclear. At present, cirrhotic cardiomyopathy can be defined as the constellation of one or more of these following factors[74]:

- Normal or increased left ventricular systolic contractility at rest, but attenuated systolic or diastolic responses to stress stimuli,
- Structural or histological changes in cardiac chambers,
- Electrophysiological abnormalities such as prolonged electrocardiographic QT interval,
- Serum markers suggestive of cardiac stress.

<u>Systolic dysfunction</u>

Despite the increased or normal cardiac output at rest, under physiological stress cirrhotic patients fail to mount an adequate stimulatory cardiac response. Gould et al documented in cirrhotic patients that with exercise the left ventricular end-diastolic and pulmonary arterial pressures

increased with no change in the cardiac index. In other words, cardiac output did not increase despite increased ventricular filling pressures, which indicates a highly impaired ventricular response[91]. Similarly Grose et al showed that when cirrhotic patients underwent maximal exercise, cardiac output increased by only 97%; this is considered inadequate when compared to approximately 300% increase in healthy controls[92]. Similar blunted cardiac systolic response to exercise was also demonstrated by Wong et al[93]; moreover patients with ascites showed greater dysfunction than those with preascitic cirrhosis.

The cardiac response to different physiological stimuli, including Valsalva's maneuver, ice-cold skin stimulation, and mental stress was investigated by Lunzer et al and found to be inadequate[94]. Lee and colleagues showed an inappropriate decrease in the cardiac output in the postprandial state in cirrhotic patients[95]. Blunted cardiac responsiveness has been reported in response to other pharmacological agents. Limas et al showed that angiotensin infusion in cirrhotics resulted in an increase in the pulmonary wedge pressure, which reflects left ventricular filling pressure, without any change in the cardiac output[96]. Blunted cardiac responsiveness has also been documented in response to catecholamine infusions[97].

Diastolic dysfunction

Diastolic dysfunction is thought to be more prevalent in cirrhotic patients[98]. This is manifested by a stiff, noncompliant ventricle that impairs diastolic filling. Finucci et al compared the diastolic function in 42 cirrhotic patients with 16 healthy controls. The cirrhotic patients had increased left ventricular end-diastolic and left atrial volumes, stroke volume, and late diastolic flow velocity compared to normal controls; these results indicate an impaired left ventricular relaxation in the cirrhotic patients[98]. A widely-used index of diastolic function is the echocardiographic E/A ratio. This is the velocity of the diastolic early filling wave (E) divided by the velocity of the late (or atrial) filling wave (A). Normally, this ratio is >1. Many studies have demonstrated a low E/A in patients with cirrhosis[99].

Structural/histological changes

Multiple studies were conducted to evaluate the heart mass in patients with liver cirrhosis. Most studies did not show any significant structural changes in liver cirrhotic patients[100]. However, some have reported changes of left ventricular hypertrophy in both humans and in portal hypertensive rats[84]. Studies evaluating the heart mass using echocardiography reported enlarged left atrial volumes with normal ventricular volumes[101]. Others

however, reported increases in both the end-diastolic and end-systolic volumes of the left ventricle[102]. Changes involving the right heart chambers are less pronounced and were normal in most studies[103]. These cardiac changes may be related to the hyperdynamic circulation of cirrhosis and were correlated with its severity in some studies. The presence of cardiac histological changes has been described in several autopsy studies. Findings include myocardial hypertrophy, cardiomyocyte edema, fibrosis, nuclear vacuolation, and unusual pigmentation[103]. However, these changes were reported from studies dating back at least 50 years in patients suffering from alcoholic cirrhosis. Lunseth et al studied the autopsies of 108 patients with cirrhosis from all causes (although most were alcoholic) and demonstrated the same cellular myocardial abnormalities that were described in earlier studies[104]. Other studies conducted on animal models including some of our work on long-term bile duct ligated cirrhotic rats failed to show any histological changes by light microscopy[105]. This discrepancy between the histological changes in human and animal studies is probably related to the long disease duration in cirrhotic patients versus the much shorter periods needed to induce cirrhosis in animal models.

Electrophysiological abnormalities

QT prolongation has been described in patients with liver disease and is significantly related to the severity of the underlying liver disease[106]. However, significant ventricular arrhythmias and sudden cardiac death remain uncommon. The prolonged QT interval is thought to revert to normal following improvement in liver function and liver transplantation[107]. The effect of β-adrenergic blockade on the prolonged QT interval in cirrhotic patients was also evaluated and was found to reduce the prolonged QT interval towards normal[108]. Henriksen et al examined the temporal relation between electrical and mechanical systole in patients with liver cirrhosis and in addition to the prolonged QT interval in their study population they also showed alteration in the cardiac excitation-contraction temporal relationship[109]. In conclusion the prolonged QT interval is well linked to liver disease and is a feature of cirrhotic cardiomyopathy. Its exact mechanism and its prognostic significance require further study.

Serum markers

Cardiac troponin I and the family of natriuretic peptides were noted to be elevated in cirrhotic cardiomyopathy, possibly reflecting the underlying myocardial strain. Atrial natriuretic peptides (ANP) are released mainly by

the atria in response to stretch, and brain or B-type natriuretic peptide (BNP) by the ventricles[110]. Troponin I increases in conditions leading to ventricular hypertrophy or dilatation. Pateron et al showed an increased serum troponin I level in about 1/3 of cirrhotic patients. Elevated levels correlated with decreased ventricular stroke volume index[111]. In cirrhotic patients, BNP levels correlated significantly with septal thickness and end-diastolic left ventricular diameter[112,113]. These results suggest the potential role of these markers for screening patients with cirrhosis for the presence of cirrhotic cardiomyopathy, and thereby identifying such patients for further investigations.

Echocardiography

Echocardiography increasingly has become a key component in the routine evaluation of patients with suspected or known cardiovascular disease. Two-dimensional (2D) echocardiography is able to visualize the heart directly in real time using ultrasound, providing instantaneous assessment of the myocardium, cardiac chambers, valves, pericardium, and great vessels. Doppler echocardiography measures the velocity of moving red blood cells and has become a noninvasive alternative to cardiac catheterization for assessment of hemodynamics.

2D echocardiography is an ideal imaging modality for assessing left ventricular (LV) size and function. 2D echocardiography is useful in the diagnosis of LV hypertrophy and is the imaging modality of choice for the diagnosis of hypertrophic cardiomyopathy. Other chamber sizes are assessed by visual analysis, including the left atrium and right-sided chambers.

Doppler echocardiography uses ultrasound reflecting off moving red blood cells to measure the velocity of blood flow across valves, within cardiac chambers, and through the great vessels. Normal and abnormal blood flow patterns can be assessed noninvasively. Color-flow Doppler imaging displays the blood velocities in real time superimposed upon a 2D echocardiographic image. Doppler echocardiography allows noninvasive evaluation of ventricular diastolic filling. The transmitral velocity curves reflect the relative pressure gradients between the left atrium and ventricle throughout diastole. They are influenced by the rate of ventricular relaxation, the driving force across the valve, and the compliance of the ventricle. There is a progression of diastolic dysfunction, which can be assessed by Doppler flow velocity curves. In the early phase of diastolic dysfunction there is primarily an impairment of LV relaxation, with reduced early transmitral flow and a compensatory increase in flow during atrial contraction. As disease progresses, and ventricular compliance declines, left

atrial pressure rises, resulting in a higher early transmitral velocity and shortening of the deceleration of flow in early diastole so that the filling pattern becomes normal, termed pseudonormalization. In patients with the most severe diastolic dysfunction and further elevation of left atrial pressure, early diastolic flow velocity rises further, termed the restrictive filling pattern. The addition of analysis of Doppler tissue velocities of annular motion provides further information concerning the diastolic properties.

The systolic function is evaluated with the following parameters in echocardiography.

- Ejection fraction
    - Simpson's apical biplane method is recommended as the accurate echo measure of LVEF.
- Fractinal shortening at endocardium and midwall
- Stress-shortening relations
- Pressure volume analysis

The prevalence and extent of systolic dysfunction in cirrhotic patients variable. If present, it is unlikely to manifest itself without a stimulus. Stroke volume and contractile indices such as dP/dt (first derivative of ventricular pressure generation) typically are normal or even increased at rest.

Conventional Doppler echocardiography is the method of choice in assessment of diastolic function. The peak velocities of LV filling during the early rapid (E wave), atrial contraction (A wave) phases, the ratio of the 2 filling velocities (E/A ratio), E wave deceleration time and the isovolumetric relaxation time are recorded at end-expiration for 5 consecutive beats at baseline and again during the phase of Valsalva maneuver.

Diastolic dysfunction represents a decrease in left ventricular filling and reduced possibility to maintain stroke volume without a compensatory increase of atrial filling pressures. This condition usually precedes the development of systolic dysfunction and is the main determinant of heart failure. Diastolic dysfunction appears to be more prevalent in patients with cirrhotic cardiomyopathy.

Electrocardiogram

The electrocardiogram is a graphic recording of electric potentials generated by the heart. The signals are detected by means of metal electrodes attached to the extremities and chest wall and are then amplified and recorded by the electrocardiograph. ECG leads actually display the instantaneous differences in potential between these electrodes.

Electrophysiological changes including prolonged depolarization and impaired cardiac excitation-contraction coupling been demonstrated in cirrhotic patients. Repolarization prolongation manifested by a prolonged QT interval (more than 440 msec) on the electrocardiogram is found in 30–50% of patients with cirrhosis. Severity of liver disease seems to be correlated to the degree of QT prolongation. These changes disappear after liver transplantation in most patients.

AIM OF THE STUDY

1. To study the cardiac dysfunction in cases diagnosed with cirrhosis of liver of nonalcoholic etiology

2. To study the conduction disturbances in cases diagnosed with cirrhosis of liver of nonalcoholic etiology

3. To assess the relationship between the severity of cirrhosis and the presence of cirrhotic cardiomyopathy

4. To assess the relationship between ascites and the presence of cirrhotic cardiomyopathy

MATERIALS AND METHODS

Patients included in the study were recruited from the Department of Digestive Health and Diseases, Government Peripheral hospital, Anna Nagar, Chennai. The study period was from July 2006 to April 2009.

Inclusion criteria

Consecutive patients diagnosed to have cirrhosis of nonalcoholic etiology formed the study group.

Exclusion criteria

Cases with the following features were excluded from the study –

- Cases who are alcoholics
- Cases with severe ascites
- Cases who have coronary artery disease
- Cases who have risk factors for cardiomyopathy other than cirrhosis
- Cases with history of recent bleed
- Cases with severe anemia
- Cases who are hypertensive
- Cases who are diabetics

Investigations done include complete blood count, liver function test, ultrasound scan of the abdomen along with Doppler scan, viral markers, ascitic fluid analysis, liver biopsy, electrocardiography, and echocardiography. The parameters that were assessed in echocardiography are E/A ratio, end diastolic volume (EDV), end systolic volume (ESV), ejection fraction.

QTc interval more than 440 msec and E/A ratio less than 1 were considered diagnostic of cirrhotic cardiomyopathy in this study. End diastolic volume of 90, end systolic value of 38 and ejection fraction of 60% were considered mean of the normal values while doing statistical analysis.

The statistical analysis was done using SSPS software version 15. Univariate and multivariate analysis were done with Chi Square test. P value of < 0.05 was found to be significant. Percentage calculation was done whenever appropriate.

RESULTS

The total number of cases included in this study was 30. Of these, there were 22 females and 8 males.

Sex distribution

Sex	Frequency	Percentage
Female	22	73.33
Male	8	26.67
Total	30	100.00

Of the 30 cases included in this study 10 patients were below 40 years of age, 11 cases were between 40 and 50 years of age and 9 cases were above 50 years of age.

Age distribution

Age group in years	Frequency	Percentage
Below 40 years	10	33.33
40-50 years	11	36.67
Above 50 years	9	30.00
Total	30	100.00

In 12 cases, cirrhosis was due to hepatic B viral infection, 1 due to hepatitis C, 1 due to primary biliary cirrhosis and in 16 patients it is idiopathic.

Etiology

Etiology	Frequency	Percentage
Hepatitis B virus	12	40.00
Hepatitis C virus	1	3.3%
Primary Biliary Cirrhosis	1	3.3%
Idiopathic	16	53.3%
Total	30	100

Clinical findings

Of the 30 cases included in the study, 24 cases had ascites (80%). 25 cases had varices (83.33%). 20 cases (66.77%) had Class A Child Turcotte Pugh Score. 10 cases (33.33%) had Class B Child Turcotte Pugh Score. There were no cases which belonged to Class C of CTP scoring who had cirrhosis.

Child Turcotte Pugh Class

CTP Class	Frequency	Percentage
Class A	20	66.67
Class B	10	33.33
Total	30	100.00

Ascites

Ascites	Frequency	Percentage
Present	24	80.00
Absent	6	20.00
Total	30	100.00

Varices

Varices	Frequency	Percentage
Present	25	83.33
Absent	5	16.67
Total	30	100.00

Conduction disturbances

Out of the 30 cases who were included in the study, 16 patients had QTc interval of more than 440 msec. Of these 16 patients 11 were males and 5 were female patients.

QTc interval

QTC value	Frequency	Percentage
Above 440 msec	16	53.33
Below 440 msec	14	46.67
Total	30	100.00

QTc interval above 440 msec and sex distribution

Sex	Frequency	Percentage
Males	11	68.75
Females	5	31.25
Total	16	100.00

Left ventricular dysfunction

Out of the 30 cases, the ratio of early diastolic and late diastolic filling velocity (E/A ratio) was less than 1 in 25 cases. Of these 25 cases 19 were females and 6 were males.

E/A ratio

Value	**Frequency**	**Percentage**
Below 1	25	83.33
Above 1	5	16.67
Total	30	100.00

E/A ratio less than 1 and sex distribution

Sex	**Frequency**	**Percentage**
Males	6	24.00
Females	19	76.00
Total	25	100.00

Out of the 30 cases included in this study 26 patients had features cirrhotic cardiomyopathy. These cases had a prolonged QTc interval of more than 440 msec or an E/A ratio of less than 1. Of these 26 cases, 8 were males and 18 were females.

Cirrhotic cardiomyopathy

	Frequency	Percentage
Present	26	86.67
Absent	4	13.33
Total	30	100.00

Cirrhotic cardiomyopathy and sex distribution

Sex	Frequency	Percentage
Males	8	30.00
Females	18	70.00
Total	26	100.00

Of the 30 patients included in this study, 14 patients had end diastolic volume above 90. 3 patients had end systolic volume above 38. 29 patients had ejection fraction above 60%.

End diastolic volume

End diastolic volume	Frequency	Percentage
Above 90	14	46.67
Below 90	16	53.33
Total	30	100.00

End systolic volume

End systolic volume	Frequency	Percentage
Above 38	3	10.00
Below 38	27	90.00
Total	30	100.00

Ejection fraction

Ejection fraction	Frequency	Percentage
Above 60	29	96.67
Below 60	1	3.33
Total	30	100.00

Statistical analysis

Out of the 30 cases, 26 showed features of cirrhotic cardiomyopathy. 20 patients had Class A Child Turcotte Pugh score. 10 patients had Class B Child Turcotte Pugh score. 16 patients with cirrhotic cardiomyopathy had Class A Child Turcotte Pugh score. 10 patients with cirrhotic cardiomyopathy had Class B Child Turcotte Pugh score. 4 patients with Class A Child Turcotte Pugh score did not have cirrhotic cardiomyopathy. The ‘p’ value of this association between Child Turcotte Pugh score and

cirrhotic cardiomyopathy is 0.128 and it is not significant. This implies that cirrhotic cardiomyopathy is not influenced by the class of Child Turcotte Pugh score.

	Cardiomyopathy present	**Cardiomyopathy absent**	**Total**
Class A CTP score	16 (80%)	4 (20%)	20 (66.7%)
Class B CTP score	10 (100%)		10 (33.3%)
Total	26 (86.7%)	4 (13.3%)	30 (100%)
			P value = 0.336

	Class A CTP score	Class B CTP score	Total
Cirrhotic cardiomyopathy Present	16 (61.5%)	10 (38.5%)	26 (86.7%)
Cirrhotic cardiomyopathy Absent	4 (100%)		4 (13.3%)
			P value = 0.128

24 of the 30 cases had ascites. Of the 26 cases that had cirrhotic cardiomyopathy 24 cases had ascites. All the cases that had ascites showed features of cirrhotic cardiomyopathy. 2 cases without ascites also showed features of cirrhotic cardiomyopathy. 4 of the 30 cases did not show features of cirrhotic cardiomyopathy. All these 4 cases did not have ascites. The 'p' value of the association of ascites and cirrhotic cardiomyopathy is 0.0002 and it is significant. This implies presence of ascites is a significant finding in cases who have cirrhotic cardiomyopathy.

	Cardiomyopathy present	**Cardiomyopathy absent**	**Total**
Ascites Present	24 (100%)		24 (80%)
Ascites Absent	2 (33.3%)	4 (67.7%)	6 (20%)
Total	26(86.7%)	4 (13.3%)	30 (100%)
			P value = 0.0002

	Ascites Present	**Ascites absent**	**Total**
Cirrhotic cardiomyopathy Present	24 (92.3%)	2 (7.7%)	26 (86.7%)
Cirrhotic cardiomyopathy Absent		4 (100%)	4 (13.3%)
			P value = 0.0002

25 of the 30 cases had varices. Of the 26 cases that had cirrhotic cardiomyopathy, 21 had varices. 4 cases with varices did not have cirrhotic cardiomyopathy. 5 cases with cirrhotic cardiomyopathy did not have varices. 4 cases did not have cardiomyopathy. All these 4 cases had varices. The 'p' value of the association between cirrhotic cardiomyopathy and varices is 0.336 and it is not significant. This implies presence of varices is not a significant finding in cases that have cirrhotic cardiomyopathy.

	Cardiomyopathy present	**Cardiomyopathy absent**	**Total**
Varices Present	21 (84%)	4 (16%)	25 (83.3%)
Varices Absent	5 (100%)		5 (16.7%)
Total	26(86.7%)	4 (13.3%)	30 (100%)
			P value = 0.336

	Varices Present	**Varices absent**	**Total**
Cirrhotic cardiomyopathy Present	21 (80.8%)	5 (19.2%)	26 (86.7%)
Cirrhotic cardiomyopathy Absent	4 (100%)		4 (13.3%)
			P value = 0.336

The QTc interval was more than 440 msec in 11 females and 5 males. It was below 440 msec in 11 females and 3 males. 68% of those who had QTc above 440 msec were females. Similarly 78% of those who had QTc below 440 msec were females. 50% of the 22 females had QTc above 440

msec. 62.5 of the 8 males had QTc above 440 msec. These associations have a 'p' value of 0.543 which is not significant. This implies prolongation of QTc interval is not a significant finding in patients who are cirrhotics. Similarly the prolongation of QTc interval is not influenced by sex.

Sex	**QTc above 440 msec**	**QTc above 440 msec**	**Total**
Female	11 (50%)	11 (50%)	22 (73.3%)
Male	5 (62.5%)	3 (37.5%)	8 (26.7%)
Total	16 (53.3%)	14 (46.7%)	30 (100%)
			P value = 0.543

	Female	**Male**	**Total**
QTc interval Above 440 msec	11 (68.8%)	5 (31.2%)	16 (53.3%)
QTc interval Below 440 msec	11 (78.6%)	3 (21.4%)	14 (46.7%)
			P value = 0.543

Out of the 30 patients, 26 showed features of cirrhotic cardiomyopathy.

14 patients had end diastolic volume above 90. 16 patients had EDV below 90. 12 patients with diastolic dysfunction had EDV above 90. 14 patients with diastolic dysfunction had EDV below 90. 2 patients with EDV above 90 did not have diastolic dysfunction.

The 'p' value of this association between EDV and diastolic dysfunction is 0.885 and it is not significant.

This implies that abnormality of EDV is not a significant feature of cirrhotic cardiomyopathy.

	Diastolic dysfunction Present	Diastolic dysfunction Absent	Total
EDV > 90	12 (85.7%)	2 (14.3%)	14 (46.7%)
EDV < 90	14 (87.5%)	2 (12.5%)	16 (53.3%)
Total	26 (86.7%)	4 (13.3%)	30 (100%)
			P=0.885

	EDV > 90	EDV < 90	Total
Diastolic dysfunction present	12 (46.2%)	14 (53.8%)	26 (86.7%)
Diastolic dysfunction absent	2 (50%)	2 (50%)	4 (13.3%)
			P value = 0.885

3 cases had end systolic volume above 38. 27 cases had ESV below 38. 2 cases with diastolic dysfunction had ESV above 90. 22 cases with diastolic dysfunction had ESV below 38. 1 case with ESV above 38 did not have diastolic dysfunction. 3 cases without diastolic dysfunction had ESV below 38. The 'p' value of this association between ESV and diastolic dysfunction is 0.282 and it is not significant. This implies that abnormality of ESV is not a significant feature of cirrhotic cardiomyopathy.

	Diastolic dysfunction present	Diastolic dysfunction Absent	Total
ESV > 38	2 (66.7%)	1 (33.3%)	3 (10%)
ESV < 38	24 (88.9%)	3 (11.1%)	27 (90%)
Total	26 (86.7%)	4 (13.3%)	30 (100%)
			P value = 0.282

	ESV > 38	ESV < 38	Total
Diastolic dysfunction present	2 (7.7%)	24 (92.3%)	26 (86.7%)
Diastolic dysfunction absent	1 (25%)	3 (75%)	4 (100%)
			P value = 0.282

29 cases had ejection above 60. 3 patients had EF below 60. 25 patients with cirrhotic cardiomyopathy had EF above 60. 1 case with diastolic dysfunction had EF below 60. 4 patients with EF above 60 did not have diastolic dysfunction. The 'p' value of this association between EF and diastolic dysfunction is 0.689 and it is not significant. This implies that abnormality of EF is not a significant feature of cirrhotic cardiomyopathy.

	Diastolic dysfunction present	Diastolic dysfunction Absent	Total
EF > 60	25 (86.2%)	4 (13.8%)	29 (96.7%)
EF < 60	1 (100%)		1 (3.3%)
Total	26 (86.7%)	4 (13.3%)	30 (100%)
			P value = 0.689

	EF > 60	EF < 60	Total
Diastolic dysfunction present	25 (96.2%)	1 (3.8%)	26 (86.7%)
Diastolic dysfunction absent	4 (100%)		4 (13.3%)
		P value = 0.689	

DISCUSSION

In this study 12 cases had cirrhosis due to HBV infection, 1 due to HCV infection, 1 due to primary biliary cirrhosis and in 16 it was idiopathic. Features of cirrhotic cardiomyopathy were present in 26 out of the 30 cases. Cirrhotic cardiomyopathy was found in patients with all the etiologies. In a study done by Torregrosa M et al[114], it was found that the cardiac changes in cirrhosis are independent of the etiology of cirrhosis. Lunzer et al[115] in their study found that cardiac dysfunction in cirrhotics did not correlate with the etiology of the cirrhosis. Our study also showed that the presence of cirrhotic cardiomyopathy was independent of the etiology.

Of the 30 cases included in this study, 22 were females and 8 were males. Of the 22 females 18 had features of cirrhotic cardiomyopathy. All the eight males had features of cirrhotic cardiomyopathy. This study showed there is no significance between sex distribution and that features of cirrhotic cardiomyopathy is present in most of the cirrhotics. Liu et al[13] in their study found that some amount of diastolic dysfunction is seen in almost all cirrhotics.

In our study 33.3% of the cases were below 40 years and 66.7% above 40 years. The four patients who were not showing features of cirrhotic cardiomyopathy were below 40 years. It was statistically significant and implied that the presence of cirrhotic cardiomyopathy is influenced by age and is more prevalent in older individuals. Rabie et al[116] in their study found that diastolic dysfunction seen in cirrhosis is associated with older age which is similar to the finding of our study.

80% of the cases had ascites at presentation. All the cases who presented with ascites had features of cirrhotic cardiomyopathy. 33.33% of the cases who did not have ascites had features of cirrhotic cardiomyopathy. On the other hand 92.3% of the patients with cirrhotic cardiomyopathy had ascites and 7.7% did not have ascites. This shows that presence of ascites correlates significantly with the presence of cirrhotic cardiomyopathy ('p'=0.0002). Wong et al[117] have found that diastolic dysfunction may be a significant factor in the development of heart failure, may precede systolic dysfunction in patients with cirrhosis, and may play a part in the pathogenesis of sodium fluid retention in cirrhosis and thus related to ascites. Pozzi et al[118] in their study have found that irrespective of ascites and cause, advanced cirrhosis is associated with left ventricle diastolic dysfunction. But in our study ascites was a significant feature of all cases

with diastolic dysfunction. Lee et al[13] found that once cirrhosis has advanced to a moderate stage with the development of ascites some degree of diastolic dysfunction is always present.

66.7% of the cases had CTP Class A cirrhosis. 33.3% of the cases had Class B cirrhosis. 80% of Class A had features of cirrhotic cardiomyopathy. All the cases with Class B had features of cirrhotic cardiomyopathy. 61.5% of the cases with cirrhotic cardiomyopathy had Class A cirrhosis. 38.5% had Class B cirrhosis. 20% of Class A and 13.3% of Class B cirrhosis did not have features of cirrhotic cardiomyopathy. The severity of cirrhosis as based on CTP does not correlate with the presence of cirrhotic cardiomyopathy ('p'= 0.336). Bernardi et al[119] in their found that the frequency of cardiac dysfunction was dependent on the severity of cirrhosis as assessed by Child Turcotte Pugh score. Similar observation was done by Rabie et al[116] in their study on diastolic dysfunction in cirrhotics. But in our study no such correlation was found.

55.3% of the cases had QTc interval above 440 msec. Of these 68.8% were females and the rest males. Of the 22 females included in the study 50% had QTc interval above 440 msec. Of the 8 males included in the study 62.5% had prolonged QTc interval. These findings show that sex is not a factor in influencing the prolongation of QTc interval in cirrhotics ('p'=

0.543). Bader Faiyaz Zuberi et al[120] in their study conducted in cirrhotics from Pakistan have found that QTc were significantly higher in cirrhotic patients as compared with non-cirrhotic controls. Similarly Bernardi et al[119] found that QTc interval was significantly prolonged in cirrhotic patients when compared with healthy individuals. Lehman[121] found that prolonged QTc interval was seen more in female cirrhotics. But this study did not show any such correlation.

46.7% of the cases had end diastolic volume above 90. 85.7% of the cases with EDV above 90 had E/A ratio below 1. 87.5% of cases with EDV below 90 also had E/A ratio below 1. 46.2% of the cases with E/A ratio below 1 had EDV above 90. 53.8% of the cases with E/A ratio below 1 had EDV below 90. These findings indicate that end diastolic volume is not significant indicator of diastolic dysfunction ('p' = 0.885). Alexander Jacob et al[122] in their study done in Asian population with cirrhosis have found that end diastolic volume is not statistically significant in them. Kelbaek et al[123] in their study have found that the left ventricular end diastolic volume is normal in cirrhotics. Rectar et al[124] found that the size of the left ventricle was normal in cirrhotics. Laffi et al[125] in their study have found that left ventricular end diastolic volume is increased in cirrhotic patients.

10% of the cases had end systolic volume above 38. 66.7% of the cases with ESV above 38 had E/A ratio below 1. 88.9% of the cases with ESV below 38 also had E/A ratio below 1. 7.7% of the cases with E/A ratio below 1 had ESV above 38. 25% of the cases with E/A ratio above 1 also had ESV above 38. These findings indicate that end systolic volume is not significant indicator of cardiac dysfunction ('p' = 0.282). Alexander Jacob et al in their study done in Asian population with cirrhosis have found that end systolic volume is not statistically significant in them. Kelbek et al in their study have found that the left ventricular end systolic volume is normal in cirrhotics. Rectar et al found that the size of the left ventricle was normal in cirrhotics. Laffi et al in their study have found that left ventricular end systolic volume is increased in cirrhotic patients.

96.7% of the cases had ejection fraction above 60%. 86.2% of the cases with EF above 60 had E/A ratio below 1. 96.2% of the cases with E/A below 1 had EF above 60. All the cases that had E/A ratio above 1 also had EF above 60. These findings indicate that ejection fraction is not significant indicator of cardiac dysfunction ('p' = 0.689). Alexander Jacob et al in their study done in Asian population with cirrhosis have found that ejection fraction is not statistically significant in them.

CONCLUSION

- Cirrhotic patients with non alcoholic etiology do have evidence of cirrhotic cardiomyopathy. They have features in the form of diastolic dysfunction and prolonged QTc interval. Diastolic dysfunction is manifested as E/A ratio less than 1.
- The presence of cirrhotic cardiomyopathy was independent of the etiology.
- Some degree of diastolic dysfunction is seen in almost all cirrhotics.
- Diastolic dysfunction seen in cirrhosis is associated with older age.
- Ascites is a significant feature of all cases with diastolic dysfunction.
- The severity of cirrhosis does not correlate with the presence of diastolic dysfunction
- Prolongation of QTc interval is influenced by the sex of the cirrhotic individuals
- Ventricular end diastolic volume, end systolic volume and ejection fraction are not significantly affected in cirrhotic individuals.

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